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in liposomes containing lipid A have been shown to induce humoral effectors (i.e., antigen-specific antibodies), and some have been shown to induce cell-mediated responses as well. Generation of an immune response and immunoprotection in an animal vaccinated with a malaria antigen may be assayed by immunofluorescence to whole, fixed malaria sporozoites or CTLs killing of target cells transfected with CSP.

### IN THE CLAIMS

Kindly enter the following amended claims.

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1. (Amended Twice) A method of inducing an immune response comprising:  
(a) applying a formulation to intact skin of an organism, wherein the formulation comprises (i) at least one antigen which is derived from a pathogen and (ii) at least one adjuvant comprising an ADP-ribosylating exotoxin or derivative thereof having adjuvant activity, and an effective amount of the antigen which is not encapsulated induces the immune response;  
(b) activating a Langerhans cell with the at least one adjuvant; and  
(c) presenting the at least one antigen or epitope thereof on a cell surface of the Langerhans cell to a lymphocyte, thereby inducing the immune response in the organism.

2. (Amended Twice) The method of claim 1, wherein the formulation consists essentially of antigen and adjuvant.

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4. (Amended Twice) The method of claim 1, wherein a physical, chemical, electrical, or sonic penetration enhancer is not used.

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11. (Amended) The method of claim 1, wherein the antigen is derived from a bacterium.

12. (Amended) The method of claim 1, wherein the antigen is derived from a virus.

B4 13. (Amended) The method of claim 1, wherein the antigen is derived from a fungus or parasite.

B5 15. (Amended) The method of claim 1, wherein the formulation comprises a live or an attenuated live virus or virosome; and the antigen is expressed by the live or attenuated live virus or virosome, which is not encapsulated.

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B6 22. (Amended Twice) The method of claim 1, wherein the ADP-ribosylating exotoxin is pertussis toxin or a derivative thereof having adjuvant activity.

23. (Amended Twice) The method of claim 1, wherein the ADP-ribosylating exotoxin is cholera toxin (CT) or a derivative thereof having adjuvant activity.

24. (Amended Twice) The method of claim 1, wherein the ADP-ribosylating exotoxin is *E. coli* heat-labile enterotoxin (LT) or a derivative thereof having adjuvant activity.

25. (Amended Twice) The method of claim 1, wherein the ADP-ribosylating exotoxin is diphtheria toxin (DT) or a derivative thereof having adjuvant activity.

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B7 26. (Amended) The method of claim 1, wherein the ADP-ribosylating exotoxin is *Pseudomonas* exotoxin A or a derivative thereof having adjuvant activity.

27. (Amended) The method of claim 1, wherein the formulation is a cream or gel or emulsion or ointment.

28. (Amended Twice) A method of immunization comprising applying a formulation to intact skin of an organism, wherein the formulation consists essentially of one or more ADP-ribosylating exotoxins or derivatives thereof having adjuvant activity,

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and an effective amount of said one or more ADP-ribosylating exotoxins or derivatives thereof is not encapsulated.

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31. (Amended) A method of inducing an immune response comprising:

- (a) applying a formulation to intact skin of an organism, wherein the formulation comprises (i) at least one antigen which is derived from a pathogen and (ii) at least one ADP-ribosylating exotoxin or derivative thereof having adjuvant activity, and at least some antigen which is not encapsulated induces the immune response; and
- (b) inducing the immune response in the organism without perforating the skin, wherein the immune response is specific for the antigen.

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32. (Amended Twice) A method of inducing an immune response comprising:

- (a) applying a formulation to intact skin of an organism, wherein the formulation comprises (i) at least one antigen which is derived from a pathogen and (ii) at least one ADP-ribosylating exotoxin or derivative thereof having adjuvant activity, and at least some antigen which is not encapsulated induces the immune response;
- (b) activating an antigen presenting cell with the at least one ADP-ribosylating exotoxin or derivative thereof; and
- (c) presenting the at least one antigen or epitope thereof on a cell surface of the antigen presenting cell to a lymphocyte, thereby inducing the immune response in the organism.

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33. (Amended) A method of inducing an immune response comprising:

- (a) applying epicutaneously on an organism an effective amount of at least one antigen derived from a pathogen and which is not encapsulated,
- (b) activating a Langerhans cell underlying the organism's skin with at least one ADP-ribosylating exotoxin or derivative thereof having adjuvant activity,
- (c) signaling the Langerhans cell to migrate to a lymph node of the organism and mature into a dendritic cell, and

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(d) presenting the at least one antigen or epitope thereof on a cell surface of the dendritic cell to a lymphocyte; thereby inducing the immune response in the organism, wherein the immune response is specific for the at least one antigen.

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Kindly delete claims 36-40 without prejudice or disclaimer.

Kindly enter the following new claims.

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50 ~~41~~. (New) The method of claim 1, wherein the formulation comprises an ADP-ribosylating exotoxin derivative which is less toxic but remains immunogenic.

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51 ~~42~~. (New) The method of claim 1, wherein the formulation comprises a genetically produced derivative of ADP-ribosylating exotoxin in which ADP-ribosyl transferase activity is inactivated.

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52 ~~43~~. (New) The method of claim 1, wherein the formulation comprises a chemically produced derivative of ADP-ribosylating exotoxin in which ADP-ribosyl transferase activity is inactivated.

53 ~~44~~. (New) The method of claim 1, wherein the formulation comprises an ADP-ribosylating exotoxin B subunit.

54 ~~45~~. (New) The method of claim 1, wherein the formulation is comprised of antigen molecules as chemical or recombinant conjugates.

55 ~~46~~. (New) The method of claim 1, wherein the formulation is comprised of a single molecule containing both antigen and adjuvant properties.

56 ~~47~~. (New) The method of claim 1, wherein the formulation is comprised of at least some antigen molecules which lack adjuvant properties.

~~57~~ 48. (New) The method of claim 1, wherein the antigen has a molecular weight greater than 800 daltons.

~~58~~ 49. (New) The method of claim 1, wherein the antigen has a molecular weight greater than 1000 daltons.

~~59~~ 50. (New) The method of claim 1, wherein the antigen is a polypeptide of greater than 800 daltons molecular weight.

~~60~~ 51. (New) The method of claim 1, wherein the antigen is a polypeptide of greater than 1000 daltons molecular weight.

~~61~~ 52. (New) The method of claim 1, wherein the formulation comprises a whole organism, and the antigen is expressed by the whole organism which is not encapsulated.

~~62~~ 53. (New) A method of immunization comprising applying a formulation without lipid vesicles to intact skin of an organism, wherein the formulation is comprised of an effective amount of one or more ADP-ribosylating exotoxins or derivatives thereof having adjuvant activity.

~~63~~ 54. (New) The method of claim 53, wherein an allergic reaction is not induced by the immunization method.

~~64~~ 55. (New) The method of claim 53 further comprising applying alcohol to the intact skin prior to application of the formulation.

~~65~~ 56. (New) The method of claim 53 further comprising hydrating the intact skin prior to application of the one or more ADP-ribosylating exotoxins or derivatives thereof.

66 ~~57~~. (New) The method of claim 53, wherein the formulation is a solution or suspension.

67 ~~58~~. (New) The method of claim 53, wherein the formulation is a cream or gel or emulsion or ointment.

68 ~~59~~. (New) The method of claim 53, wherein the formulation is applied with a patch.

69 ~~60~~. (New) The method of claim 53, wherein at least one of the ADP-ribosylating exotoxins is pertussis toxin.

70 ~~61~~. (New) The method of claim 53, wherein at least one of the ADP-ribosylating exotoxins is cholera toxin.

71 ~~62~~. (New) The method of claim 53, wherein at least one of the ADP-ribosylating exotoxins is *E. coli* heat-labile enterotoxin.

72 ~~63~~. (New) The method of claim 53, wherein at least one of the ADP-ribosylating exotoxins is diphtheria toxin.

73 ~~64~~. (New) The method of claim 53, wherein at least one of the ADP-ribosylating exotoxins is *Pseudomonas* exotoxin A.

74 ~~65~~. (New) The method of claim 53, wherein the formulation comprises an ADP-ribosylating exotoxin derivative which is less toxic but remains immunogenic.

75 ~~66~~. (New) The method of claim 53, wherein the formulation comprises a genetically produced derivative of ADP-ribosylating exotoxin in which ADP-ribosyl transferase activity is inactivated.

76 ~~67~~. (New) The method of claim 53, wherein the formulation comprises a chemically produced derivative of ADP-ribosylating exotoxin in which ADP-ribosyl transferase activity is inactivated.

B12 77 ~~68~~. (New) The method of claim 53, wherein the formulation comprises an ADP-ribosylating exotoxin B subunit.

Ins C6 78 ~~69~~. (New) A method of immunization comprising hydrating intact skin of an organism; applying an effective amount of one or more ADP-ribosylating exotoxins or derivatives thereof having adjuvant activity to the hydrated, intact skin in the absence of lipid vesicles; and separately administering one or more antigens which are derived from one or more pathogens such that the organism is effectively immunized.

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**IN THE SEQUENCE LISTING**

Kindly enter the attached paper and computer readable forms of the Sequence Listing.